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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,461	12/11/2003	Michael P. Czech	UMY-055	3119
959	7590	06/12/2006	EXAMINER	
LAHIVE & COCKFIELD 28 STATE STREET BOSTON, MA 02109			SCHNIZER, RICHARD A	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/735,461

Applicant(s)

CZECH ET AL.

Examiner

Richard Schnizer, Ph. D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27 and 38-81 is/are pending in the application.
- 4a) Of the above claim(s) 60-78 and 80 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27, 38-59, 79 and 81 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/6/05; 11/10/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Examiner in charge of this Application has changed. Please direct further correspondence to Richard Schnizer, whose contact information is given at the conclusion of the Action.

An amendment was received on 3/22/06. Applicant's election without traverse of group 1 and the species "type II diabetes" is acknowledged. After further consideration, the restriction requirement between groups I and II is withdrawn. Claims 60-78 and 80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/22/06.

Claims 27, 38-59, 79, and 81 are under consideration in this Action. Claim 81 is considered only to the extent that it depends from claim 79.

Comment

Applicant may wish to substitute "adipocyte" for "cell" in claim 27 items (c) and (d), and in claim 79, items (c) and (d), to more closely parallel item (a) in these claims. A similar substitution of the term "cell" in items (a) and (b) is not recommended because "cell" in these cases, as it modifies "membrane", has the connotation of "plasma membrane" to one of ordinary skill in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 52-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is indefinite because the metes and bounds of "siRNA derivative" are unclear. It is unclear what is considered to be a "derivative" and what is not.

Claims 53-55 are indefinite because claim 53 recites "the siRNA derivative" without antecedent basis. These claims are also indefinite because they require "increased" or "decreased" stability or activity, but they set no standard against one may compare to determine whether the activity or stability is increased or decreased.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 38-59, 79, and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying a gene that affects glucose transport by contacting an isolated adipocyte with an siRNA targeted against the gene to form a mixture, electroporating the mixture, culturing the cell in vitro, and assaying glucose transport in vitro, does not reasonably provide enablement for such methods performed in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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The claims are directed to methods of identifying a gene that affects glucose transport by contacting an adipocyte with an siRNA targeted against the gene to form a mixture, electroporating the mixture, culturing the cell, and assaying glucose transport. It is not clear that the limitation "culturing the cell" limits the invention to methods performed in vitro, so the broadest reasonable interpretation of the claims includes embodiments in which the methods are carried out on adipocytes in vivo.

The specification as filed provides no guidance as to how to perform the method in vivo, in particular how to measure glucose uptake or GLUT4 translocation in vivo while distinguishing electroporated cells from non-electroporated cells, such that one of skill could draw valid conclusions from any data obtained. The prior art of record provides no guidance in this regard, and such an assay was not routinely performed in the art at the time of the invention. As a result, one of skill in the art would have to perform undue experimentation in order to practice the invention as broadly claimed. This rejection could be overcome by requiring that the recited adipocytes must be "isolated".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 38-42, and 45 are rejected under 35 U.S.C. 102(a) as being anticipated by Jiang et al (Proc. Nat. Acad. Sci. USA 100(13):7569-7574, 2003).

Jiang taught a method in which the function of Akt1 and Akt2 in glucose uptake in adipocytes was studied by siRNA inhibition. Oligonucleotides inhibiting expression of Akt1 and Akt2 were electroporated into adipocytes under conditions including 0.18 kV and 960 micro F capacitance. Glucose uptake was assayed directly, and by assay of GLUT4 translocation. See abstract; page 7570, column 1, first full paragraph; paragraph bridging columns 1 and 2 on page 7573, and paragraph bridging pages 7573 and 7574.

It is noted that this application claims priority to provisional application 60/432,427, filed 12/11/02. However, the '427 application does not support the limitations of the rejected claims (i.e. the recited ranges of voltage and capacitance in claims 38-42, and the limitation "at least 12 hours" in claim 45). These limitations are supported only in the instant application, and so the rejected claims are accorded an effective filing date of 12/11/03, which is after the publication date of Jiang et al. It is further noted that each of the instant inventors is an author on the Jiang publication, however the Jiang publication also lists authors who are not currently listed as inventors. As a result the invention was known and used by others in this country before the effective filing date of the application. This rejection may be overcome by an affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction. See MPEP 715.01(c).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 27, 44-48, 50, 51, 53-59, 79, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) in view of Clancy et al (US 20030087259).

Al Hasani taught methods of studying genes related to glucose transport. Specifically, Al-Hasani investigated the relationship between the GTPase dynamin and endocytosis of the GLUT4 glucose transporter in cultured rat adipocytes. Adipocytes were transfected with a construct for expressing an easily detectable (HA)-tagged GLUT4, and then with either constructs for over-expression of either wild type dynamin or a GTPase-negative mutant of dynamin. The effects of these dynamins on (HA)-tagged GLUT4 endocytosis after insulin treatment was measured. See abstract, paragraph bridging pages 17505 and 17506, Fig. 2 on page 17506, and Fig. 3 on page 17507.

Al Hasani did not teach the use of siRNA.

Clancy taught that the activity of a polypeptide in a cell can be controlled by several alternative means including the use of negative mutants of the protein and the

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use of antisense or siRNA directed at the mRNA encoding the protein. See summary of invention paragraph 9, detailed description paragraph 234, and claim 21.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use siRNA directed against dynamin to assess its role in the endocytosis of GLUT4. For example, one could have used anti-dynamin siRNA to down-regulate wild type dynamin activity instead using the negative dynamin mutant. This experiment would result in down regulation of the endogenous dynamin (as required by instant claim 59) and the exogenous dynamin expressed from the expression construct (as required by instant claim 58). Further, one of ordinary skill in the art appreciates that the effects of the negative dynamin mutant could be confirmed by reversing them through the use of siRNA directed against the mutant. It would have been obvious to deliver the siRNA by electroporation because Al-Hasani demonstrated that this method was suitable for delivering nucleic acids to adipocytes.

Regarding claims 44-46, the temperature of electroporation, and the time between electroporation and assay, are considered to be variables that are routinely optimized by those of ordinary skill in the art, and so are considered to be obvious.

Claims 53-55 are included in the rejection because these claims, which require increased siRNA stability, or increased or decreased siRNA activity, recite no standard against which to compare stability or activity. One of ordinary skill in the art possesses the ability to modify a given siRNA to have greater or lesser activity and stability by incorporation of a greater or lesser number of modified bases. So, any given siRNA has

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greater or lesser activity than a differently modified one. In the absence of any standard of comparison these limitations carry no weight.

Claim 58 is included in the rejection because those of ordinary skill in the art appreciate that glucose metabolism is important in a variety of human diseases including diabetes. As a result it would be obvious to perform similar experiments in human cells.

Claims 38-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) and Clancy et al (US 20030087259) as applied to claims 27, 44-48, 50, 51, 53-59, 79, and 81 above, and further in view of Paquereau et al (Anal. Biochem. 204(1): 147-151, 1992).

The teachings of Al-Hasani and Clancy are summarized above and can be combined to render obvious methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation at a potential of 0.2kV (see page 17505, column 1, second full paragraph).

The references are silent as to the capacitance setting for use in electroporation.

Paquereau taught a method of delivering nucleic acids to mammalian cells by electroporation using a potential of 0.15-0.2 kV and a capacitance of 960 micro F. These conditions minimized cell damage and increased cell survival. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the electrical potential and capacitance used in the electroporation of the cells of Al-Hasani because it was recognized in the art that these variables could affect the amount of cell damage caused by electroporation, as well as cellular survival after electroporation. In so doing, one of ordinary skill would have noted that Al-Hasani used a voltage in the range used by Paquereau, and so would have been motivated to use a capacitance in the range used by Paquereau with the reasonable expectation of obtaining minimal cellular damage and improved cellular survival. Note that Paquereau used the exact capacitance required by instant claim 43.

Claim 49 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) and Clancy et al (US 20030087259) as applied to claims 27, 44-48, 50, 51, 53-59, 79, and 81 above, and further in view of Standaert et al (J. Biol. Chem. 272(48): 30075-30082, 1997).

The teachings of Al-Hasani and Clancy are summarized above and can be combined to render obvious methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation.

The references do not teach an assay of glucose uptake.

Standaert taught method of studying the effect of a gene expression of protein kinase C zeta (PKC-zeta) on glucose transport. Assays included measurement of

GLUT4 translocation as well as glucose uptake. See abstract, paragraphs bridging pages 30078 to 30080, and Figs 7 and 8 on page 30079.

It would have been obvious to one of ordinary skill in the art at the time of the invention to extend the studies of Al-Hasani to studies of glucose uptake. One of ordinary skill in the art, interested in the effects of genes on glucose transport, would have realized that GLUT4 translocation and GLUT4 transport activity can both be used as measures of the effect of a gene product on glucose transport, and would have been motivated to use either one. However, one would have been particularly motivated to assay glucose uptake directly given that is the actual function of GLUT4, and so would provide a more accurate representation of the effects of the gene product on glucose transport.

Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Hasani et al (J. Biol. Chem. 273(28): 17504-17510, 1998) and Clancy et al (US 20030087259) as applied to claims 27, 44-48, 50, 51, 53-59, 79, and 81 above, and further in view of McSwiggen et al (US Patent 7,022,828).

The teachings of Al-Hasani and Clancy are summarized above and can be combined to render obvious methods of identifying a gene that affects glucose transport by assaying insulin-mediated GLUT4 translocation in the presence or absence of dynamin, wherein dynamin concentration is modulated through siRNA delivered by electroporation.

The references do not teach siRNA derivatives.

McSwiggen taught methods of inhibiting gene expression using siRNA, and taught that the stability of siRNA molecules could be enhanced through the use of modified bases. See and column 25, lines 58-67 claim 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use modified siRNA oligonucleotides in the invention of Al-Hasani as modified by Clancy. One would have been motivated to do so in order to enhance the function of the oligonucleotides, as taught by McSwiggen.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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A handwritten signature in black ink, appearing to read 'RS', with a long horizontal line extending to the right.

Richard Schnizer, Ph.D.
Primary Examiner
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